ARAŞTIRMA / RESEARCH REPORT
İnönü Üniversitesi Tıp Fakültesi Dergisi 2012;19(2):66-70.

C-Reactive Protein is not an Independent Risk Factor for Ventricular Thrombus

Orhan Saim Demirtürk[1], Öner Gülcan[1], İsa Coşkun[1], Rıza Türköz[1]

[1] Başkent Üniversitesi Adana Uygulama ve Araştırma Merkezi, Kalp-Damar Cerrahisi Bölümü, Adana

Başvuru Tarihi: 19.12.2011
Kabul Tarihi: 20.02.2012

DOI: 10.7247/jiumf.19.2.1

C-reactive protein (CRP) is a standard and widely used acute phase reactant. It is a prototypic marker of inflammation and an adverse event indicator. Elevated CRP levels have been found to be correlated with higher risk for potential adverse cardiac events in patients with acute myocardial infarction, stable and unstable coronary artery disease. However the relationship between presence of left ventricular thrombus (LVT) and levels of CRP have not been investigated in the patients undergoing left ventricular restorative operations. In order to investigate the correlation and seek out the ability of the predictive value of CRP levels in patients with left ventricular aneurysm (LVA), we studied operational and biochemical findings of our patients with LVA, who underwent coronary revascularization operations. We found that CRP levels do not predict presence of LVT.
Key Words: C-Reactive Protein; Left Ventricular Aneurysm; Left Ventricular Restoration; Coronary Revascularization.

C-Reaktif Protein Ventriküler Trombus Varlığı İçin Bağımsız Bir Risk Faktörü Değildir!

C-reaktif protein (CRP) yaygın kullanılan ve standart bir akut faz reaktanıdır. Yüksek CRP değerlerinin akut miyokard enfarktüsü, stabil ve anstabil koroner arter hastalığında ileride oluşabilecek olumsuz (advers) kardiyak olaylarda ilişkili olduğu gösterilmiştir. Ancak sol ventrikül onarımları yapılan hastalarda sol ventrikül trombüsü (SVT) ve CRP değerleri arasında bir ilişkinin varlığı araştırılmamıştır. Biz böyle bir korelasyonun var olup olmadığını ve sol ventrikül anevrizması (SVA) olan hastalardan alınan CRP değerlerinin trombüs varlığı konusundaki prediktif değerlerini araştırmak için SVA olup koroner revaskülarizasyon ameliyatına giden hastalarımızın cerrahi ve biyokimyasal verilerini gözden geçirdik. CRP değerlerinin SVT varlığı üzerinde önceden belirleyici (prediktif) değerinin olmadığını tespit ettik.
Anahtar Kelimeler: C-Reaktif Protein; Sol Ventrikül Anevrizması; Sol Ventrikül Onarımı; Koroner Revaskülarizasyon.

Introduction

C-reactive protein (CRP) is a standard and widely used acute phase reactant.[1] CRP is a prototypic marker of inflammation and an adverse event indicator. It is a pentraxin type of protein comprising of 5 noncovalently associated protomers arranged symmetrically around a central pore with a moleculat weight of 118000 Daltons.[2] Its gene has been mapped to chromosome 1. Its role is in clearing necrotic cells. It is mostly synthesized in hepatocytes and arterial plaque tissue. Tissue injuries up-regulate its production.[3] It is transcriptionally driven by interleukin-6 and enhanced by interleukin-1.[2] CRP promotes innate immunity by binding complement factor C1q to activate the classical complement pathway.[4]

Carrespondenence: . Orhan Saim DEMİRTÜRK Başkent Üniversitesi Adana Uygulama ve Araştırma Merkezi, Kalp-Damar Cerrahisi Bölümü, ADANA
Telefon: 0 322-3272727-1143
Fax: 0 322 327 12 76-Cep: 0 532 593 52 60
e-mail: osdemirturk@yahoo.com

Elevated CRP levels have been found to correlate with higher risk for future adverse cardiac events in patients with acute myocardial infarction[5,6] stable and unstable coronary artery disease.[7,8] and peripheral arterial reconstruction[9] CRP is an independent predictor of cardiovascular risk.[10] CRP is also an independent predictor of mortality and myocardial infarction in otherwise healthy people[11].

In their work investigating the relation between left ventricular thrombus (LVT) and peak CRP levels Seo et al found that peak CRP concentrations in a cohort of 75 patients correlated positively with the presence of LVT with the first acute myocardial infarction.[12] But until now there has been no report on whether a correlation existed between the presence of left ventricular thrombus and elevated levels of CRP in patients with left ventricular aneurysm (LVA) and LVT

in a cohort of patients who are candidates for left ventricular reconsructive surgery. Our study was designed to fill in this gap.

In order to investigate the correlation and seek out the ability of the predictive value of CRP levels in patients with left ventricular aneurysm (LVA) we studied operational and biochemical findings of our patients with LVA who underwent coronary revascularization operations. We wondered whether hs-CRP can help us in stratifying risk in patients with with LVA undergoing coronary revascularization operations. We wanted to test whether high-sensitivity C-reactive protein (hs-CRP) would lend prognostic information to our LVA patients who will undergo ventricular restoration operations.

We hypothesized that if CRP plays an important role in thrombus development we should be detecting high levels of hs-CRP on admission day in patients with left ventricular thrombus (LVA). Thus we designed a partially retrospective study in which we correlated hs-CRP levels with presence of LVT in patients with LVA undergoing restorative surgical procedures. Our study investigated whether CRP is an independent predictor of LVT.

Patients and Methods

To test our hypothesis we enrolled past patients operated on for LVA in our clinic retrospectively and added new patients who fulfilled our inclusion criteria prospectively. Preoperative clinical and demographic, angiographic and biochemical data and perioperative findings were investigated in 100 consecutive retrospective and prospective patients aged between 38 to 82 years in patients undergoing coronary revascularization with LVA who required ventricular restoration techniques.

Hs-CRP levels were determined at admittance to hospital for operation and were related to presence or absence of LVT in patients undergoing operation for LVA and myocardial revascularization.

Exclusion criteria

Age>85 years, emergency revascularizations, left ventricular ejection fraction < 20%, previous cerebrovascular accident with permanent disability, presence of active infection, hemorrhagic conditions, patients under chronic dialysis program, presence of collagen vascular diseases and other vasculitides, patients under chronic antinflammatory therapy constituted our patient exclusion criteria.

Patient characteristics

Of the 88 patients who were enrolled in our study 12 were female and 66 were male. The average age was 58.9±9.8 years. The average bypass greft number was 2.39±1.25. As for ventricular restoration of the 88 patients 48 underwent Dor type aneurysmectomy (54.5%), 34 underwent lineer aneurysmectomy (38.6%); 6 underwent Jatene type ventricular repair (6.8%). 49 patients underwent ventricular restoration operation using cross-clamp and blood cardioplegia (55.7%), 33 patients were operated using on-pump beating heart method (37.5%); and 6 patients were operated on the beating heart (6.8%). There were 8 additional procedures (9.1%) during the ventricular restorations. There were 5 coronary endarterectomies (5.7%), 2 Alfieri type mitral repairs (2.3%). 80 of the 88 patients (90.9%) had no additional procedures. Eighty-seven patients were operated on using midline sternotomy, one patient was operated on by lateral thoracotomy. He was a 62 year old man who had undergone a prior coronary bypass operation. He had developed a latent aneurysm which was reconstructed by us using a lateral thoracotomy. Two patients required intraaortic baloon counterpulsation (IABC) (2.3%)

Measurement of CRP

CRP levels were obtained from peripheral blood of patients on admission day which was usually the day before surgery. Immunonefelometry was used in the quantification of CRP. We measured hs-CRP using Dade Behring Acute Care Cardiophase® hsCRP kits and Dade Behring BNII® devices, Dade Behring Holding GmbH, Eschborn-Germany.

Statistical analysis

Descriptive and frequency analyses were acquired and SPSS 10 for Windows statistical program (SPSS Inc., Chicago , Illinois, USA) was used for statistical evaluation of the patients. Quantitative data were shown as mean±standard deviation of the mean. Univariate logistic regression analysis was applied to the whole group to find out whether admission CRP level was an independent predictor of left ventricular thrombus. Multivariate lineer regression analysis was used to find out whether clinically normal (< 6mg/l) and clinically supranormal (>6 mg/l) CRP levels had an effect on the presence of ventricular thrombus. P values < 0.05 were accepted as statistically significant.

Results

Univariate logistic regression analysis showed that there is no correlation between elevated levels of hs-CRP and presence of LVT in patients undergoing left ventricular restoration (p=0.711, t=0.372). This implies that hs-

CRP levels do not have predictive value in foreshadowing presence LVT. Therefore hs-CRP is not an independent risk factor of LVT in patients with LVA.

Multivariate lineer regression analysis showed that hs-CRP > 6 mg/l also did not predict the presence of LVT ($p= 0.766$, $t=0.30$).

There were 4 in-hospital mortalities (4.5%). One of these patients was the 61 year-old female patient who underwent a bilateral carotid endarterectomy as an additional procedure who passed away in the 25th postoperative day in the intensive care unit (IUC). 3 mortalities occured with pump support beating heart patients (3.2%) one of whom was a 59 year-old male patient who required an IABC that died on the 6th postoperative day in the IUC. The third mortality operated on by the pump beating method was an 80-year-old male chronic renal insufficiency patient who underwent an additional Alfieri repair procedure for ischemic mitral insufficiency. The only first day mortality was the third pump beating patient who died due to ventricular failure on the third postoperative hour in the IUC. All mortalities had comorbidities. Two had chronic obstructive pulmonary disease, two had carotid atherosclerosis one of whom was previously treated by PTCA and stenting.

Mean CRP values of the whole patient group was 11.28±16.3 mg/l. This value was 19.5±10.63 mg/l in the group with mortalities. Because of the number of patients is small in this group no attempt was made for a comparison between the two groups.

Discussion

Identification of risk markers for presence of LVT in patients with LVA could help in risk stratification and elucidating pathophysiolagical mechanisms in ventricular thrombus formation. Increased levels of hs-CRP have been related to worse outcomes in patients with acute myocardial infarction[5,6] and in unstable coronary artery disease[13] but the predictive value of hs-CRP in patients with LVA have not been thoroughly investigated.

CRP is now designated as an active participant in atherothrombosis.[2] Synthesis and secretion of CRP via paracrine and autocrine pathways by cells of the atherosclerotic region results in CRP concentrations exceeding greatly the concentrations in plasma enhancing proinflammatory and proatherogenic effects. But the assumed prothrombogenic effects of CRP has been less well evaluated.

It has been shown that CRP has both proinflammatory and prothrombotic effects by activation of tissue factor, release of interleukin 1, interleukin-6 and tumor necrosis factor.[11] There is in vivo evidence supporting these relationships in CRPtg mice that Danenberg et al. showed in which CRP concentrations reached levels as high as 18.6 mg/L compared with WT mice in whom CRP was in undetectable levels.[14] After a transluminal wire injury inflicted on the femoral artery the investigators witnessed a complete thrombotic occlusion in the femoral arteries of 75% of the CRPtg mice (CRP transgenic mice) compared with 17% of the WT (wild type) mice.[14] In this important experimantal animal model Danenberg et al. have shown us that vascular injury inflicted on mice with inherently high levels of CRP (CRP-tg mice) had a faster and higher rate of arterial thrombosis. Moreover Bisoendial et al. have demonstrated activation not only of inflammation but also of coagulation in their experiment with seven male volunteers in whom infusions of recombinant human CRP effected a rise of both markers of inflammatiom and coagulation.[10] They demonstrated that consecutive activation of coagulation was enhanced threefold manifesting itself by an increase threefold in prothrombin F1, d-dimer and plasminogen activator inhibitor type-1 concentrations.

Singh et al. demonstrated that CRP inhibits tissue plasminogen activator activity through generation of proinflammatory cytokines IL-1β and TNFα. Therefore Singh suggested that CRP is a procoagulant.[15] Therefore CRP might play a role not only in inflammation but also in atherothrombosis.[16,17] In this investigation we looked at the two phenomena from the same angle and wanted to rest our hypothesis in that direction. We had hypothesized that if CRP plays an important role in thrombus development we should be detecting high levels of hs-CRP on admission day in patients with left ventricular thrombus (LVA). We also wondered whether such a result could add some information to the relationship between inflammation and coagulation.

Activation of the coagulation cascade might result from enhanced monocytic tissue-factor activity because according to a study conducted by Cermak et al, in vitro CRP has been shown to induce monocytic tissue-factor expression.[18] In the recent past investigators like Biancari and Balciunas.[9,19] have linked high levels of preoperative hs-CRP with adverse cardiovascular events after coronary bypass grafting surgery whereas authors like Gaudino refuted this claim in their clinical observations.[1] Moreover even if such a link is valid for prothrombotic effects of CRP its molecular mechanism is controversial. In their pioneering work Cermak et al. have shown that CRP induces human peripheral blood monocytes to synthesize tissue factor (TF) which is a

key element in coagulation.[18] This view has gained general acceptance. Until recently it was generally assumed that CRP induces TF expression in human monocytes correlating inflammation, coagulation and thrombosis. However an experimental study by Paffen et al. contradicts this claim.[4] Our clinical observations are consistent with this view.

We also had thought that if a statistically significant correlation could be established between preoperative CRP levels and the presence of LVT we could add another parameter into preoperative risk scoring of patients with LVA who are candidates for ventricular reconstruction. But our study showed no such relationship exists.

Our study showed that there is no correlation between elevated levels of hs-CRP and presence of LVT in patients undergoing left ventricular restoration while being operated for purposes of myocardial revascularization. This work showed that hs-CRP levels do not have predictive value in foreshadowing presence LVT. Therefore hs-CRP is not an independent risk factor of LVT in patients with LVA. But this does not decrease the value of hs-CRP in reflecting the burden of inflammation in patients with coronary artery disease. Our study revealed that admission CRP did not predict presence of thrombus in LVA patients undergoing ventricular restoration for LVA. Such a link could not be established.

But as many of the abovementioned studies have shown CRP is not just a marker of severity of cardiovascular disease but also a potential target parameter which may aid in optimization of patients' preoperative circumstances.[20]

CRP is becoming a target marker which will be in the list of molecules that clinicians will want a significant reduction in, either for decreasing possible complications after interventions and operations or for decreasing future risks in patients clinical follow-up.

More molecular level studies are needed in the future to enlighten these controversies along with prospective studies to illuminate possible links between atherothrombosis and inflammation.

Because of the partial retrospective character of the study and the absence of CRP levels in 12 of our patients, since we could only include 88 patients for evaluation, our study was limited. But because the patient population was selected in consecutive sequence according to admission order, selection bias could be partially alleviated.

References

1. Gaudino M, Nasso G, Andreotti F, et al. Preoperative C-reactive protein level and outcome following coronary surgery. Eur J Cardio-thorac Surg 2002; 22: 521-6. DOI: 10.1016/S1010-7940(02)00436-0
2. Devaraj S, Singh U, Jialal I. The evolving rule of C-reactive protein in atherothrombosis. Clin Chem 2009; 55: 229-38. DOI: 10.1373/clinchem.2008.108886
3. Yasojima K, Schwab C, McGeer EG, McGeer PL. Generation of C-reactive protein and complement components in atherosclerotic plaques. Am J Pathol 2001; 158: 1039-51. DOI: 10.1016/S0002-9440(10)64051-5
4. Paffen E, Vos HL, Bertina RM. C-reactive protein does not directly induce tissue factor in human monocytes. Arterioscler hromb Vasc Biol 2004; 24: 975-81. DOI: 10.1161/01.ATV.0000126681.16619.69
5. Çelik S, Baykan M, Erdöl C, et al. C-reactive protein as a risk factor for left ventricular thrombus in patients with acute myocardial infarction. Clin Cardiol 2001; 24: 615-9. DOI: 10.1002/clc.4960240909
6. Anzai T, Yoshikawa T, Kaneko H, et al. Association between serum C-reactive protein elevation and left ventricular thrombus formation after first myocardial infarction. Chest 2004; 125: 384-9. DOI: 10.1378/chest.125.2.384
7. Sabatine MC, Morrow DA, Jablonski KA, et al. PEACE investigators. Prognostic significance of the centers for disease control/American Heart Association high sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation 2007; 115: 1528-36. DOI: 10.1161/CIRCULATIONAHA.106.649939
8. Versaci F, Gaspardone A, Tomai F, et al. Predictive value of C-reactive protein in patients with unstable angina pectoris undergoing coronary artery stent implantation. Am J Cardiol 2000; 85: 92-5. DOI: 10.1016/S0002-9149(99)00612-8
9. Biancari F, Lahtinen J, Lepojärvi S, et al. Preoperative C-reactive protein and outcome after coronary artery bypass surgery. Ann Thorac Surg 2003;76: 2007-12. DOI: 10.1016/S0003-4975(03)01067-1
10. Bisoendial RJ, Kastelein JJ, Levels JH, et al. Activation of inflammation and coagulation after infusion of C-reactive protein in humans. Circ Res 2005; 96: 714-6. DOI: 10.1161/01.RES.0000163015.67711.AB
11. Palmerini T, Marzocchi A, Reggiani LB, et al. Preoperative C-reactive protein levels predict 9-month mortality after coronary artery bypass surgery for the treatment of left main coronary artery stenosis. Eur J Cardiothorac Surg 2007; 31: 685-90. DOI: 10.1016/j.ejcts.2006.12.029
12. Seo Y, Maeda H, Ishizu T, et al. Peak C-reactive protein concentration correlates with left ventricular thrombus formation diagnosed by contrast echocardiographic left ventricular opacification in patients with a first anterior acute myocardial infarction. Circ J 2006; 70: 1290-6. DOI: 10.1253/circj.70.1290
13. Toss H, Lindahl B, Siegbahn A, Wallentin L, for the FRISC study group. Prognosticinfluence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. Circulation 1997; 96: 4204-10.
14. Danenberg HD, Szalai AJ, Swaminathan RV, et al. Increased thrombosis after arterial injury in human C-

reactive protein-transgenic mice. Circulation 2003; 108: 512-15. DOI: 10.1161/01.CIR.0000085568.13915.1E
15. Singh U, Devaraj S, Jialal I. C-reactive protein decreases tissue plasminogen activator activity in human aortic endothelial cells: Evidence that C-reactive protein is a procoagulant. Arterioscler Thromb Vasc Biol 2005; 25: 2216-21. DOI: 10.1161/01.ATV.0000183718.62409.ea
16. Pandolfi A. C-reactive protein: A potential new molecular link between inflammation, thrombosis and vascular cell proliferation? Cardiovasc Res 2005; 68: 3-4. DOI: 10.1016/j.cardiores.2005.07.019
17. Cirillo P, Golino P, Calabró P, et al. C-reactive protein induces tissue factor expression and promotes smooth muscle and entrhelial cell proliferation. Cardiovasc Res 2005; 68: 47-55. DOI: 10.1016/j.cardiores.2005.05.010
18. Cermak J, Key NS, Bach RR, et al. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood 1993; 82: 513-20.
19. Balciunas M, Bagdonaite L, Samalavicius R, Griskevicius L, Vuylsteke A. Pre-operative high sensitive C-reactive protein predicts cardiovascular events after coronary artery bypass grafting surgery: A prospective observational study. Ann Card Anaesth 2009; 12: 127-32. DOI: 10.4103/0971-9784.53442
20. Clearfield MB. C-reactive protein: A new risk assessment tool for cardiovascular disease. JAOA 2005; 105: 409-16.

How to cite this article: Demirtürk OS, Gülcan Ö, Coşkun İ, Türköz R. C-Reactive Protein is not an Independent Risk Factor for Ventricular Thrombus. JIUMF 2012; 19(2): 66-70. DOI: 10.7247/jiumf.19.2.1